

REVIEW ARTICLE

A Multidisciplinary and a Comprehensive Approach to Reducing Fragility Fractures in Preterm Infants

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Abstract: With advances in neonatal care, bone fractures prior to discharge from the hospital in preterm infants receiving contemporary neonatal care, are rare. Nevertheless, such fractures do occur in very low birth weight and extremely low birth weight infants who go on to develop metabolic bone disease of prematurity (MBDP), with or without secondary hyperparathyroidism. MBDP is a multifactorial disorder arising from the disruption of bone mass accrual due to premature birth, postnatal immobilisation, and loss of placental oestrogen resulting in bone loss, inadequate provision of bone minerals from enteral and parenteral nutrition, and medications that leach out bone minerals from the skeleton. All of these factors lead to skeletal demineralisation and a decrease in bone strength and an increased risk of fractures of the long bones and ribs. Secondary hyperparathyroidism resulting from phosphate supplements, or enteral/parenteral feeds with a calcium-to-phosphate ratio of < 1.3:1.0 leads to subperiosteal bone resorption, cortical thinning, and further skeletal weakening. Such fractures may occur from routine handling and procedures such as cannulation. Most fractures are asymptomatic and often come to light incidentally on radiographs performed for other indications. In 2015, we instituted a comprehensive and multidisciplinary Neonatal Bone Health Programme (NBHP), the purpose of which was to reduce fragility fractures in high-risk neonates, by optimising enteral and parenteral nutrition, including maintaining calcium-to-phosphate ratio $\geq 1.3:1$, milligram to milligram, biochemical monitoring of MBDP, safe-handling of at-risk neonates, without compromising passive physiotherapy and skin-to-skin contact with parents. The at-risk infants in the programme had radiographs of the torso and limbs at 4 weeks and after 8 weeks from enrolment into the program or before discharge. Following the introduction of the NBHP, the bone fracture incidence reduced from 12.5% to zero over an 18-month period.

Keywords: Calcium, fragility fractures, metabolic bone disease of prematurity, parathyroid hormone, parenteral nutrition, pre-term infant, phosphate.

1. INTRODUCTION

Fractures occur when the applied load exceeds the bone strength. Factors that affect bone strength include bone size

(geometry) and the amount of bone minerals contained within bone envelopes (bone mineral density). The main reasons for the decrease in bone strength in very low birth weight (VLBW; ≤ 1500 g) and extremely low birth weight (ELBW; ≤ 1000 g) infants include metabolic bone disease of prematurity (MBDP), with or without secondary hyperparathyroidism. MBDP is characterised by impaired postnatal mineralisation of the rapidly growing preterm infant's skeleton. It

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arises from inadequate mineral accrual prenatally and postnatal bone loss, resulting in diminished bone strength. Secondary hyperparathyroidism resulting from phosphate supplements or enteral/parenteral feeds with calcium to phosphate ratio of $< 1.3:1.0$ leads to subperiosteal bone resorption causing further skeletal weakening. MBDP may be asymptomatic but in severe cases, it is associated with an increased risk of fractures of the long bones and ribs. Such, fragility fractures, may occur from routine handling and procedures, such as physiotherapy and cannulation [1]. Most of the fractures are asymptomatic and often come to light incidentally on radiographs performed for other indications. Rarely, fractures may be associated with pain in handling, limb deformity, or an unexplained swelling caused by a callus.

The true incidence of fractures in VLBW and ELBW infants receiving contemporary neonatal care is unknown, as there are no studies of systematically screening for fractures using whole-body radiographs (skeletal survey). The studies from the 1980s reported an incidence of fractures in preterm infants ranging from incidences of fractures in premature infants are inconsistent ranging from 2.1% to 24% [2, 3]. Viswanathan *et al* found that in ELBW infants who survived > 8 weeks, 30.9% had radiological evidence of MBDP during their stay in the neonatal unit [4]. Furthermore, about one-third of infants with MBDP had evidence of bone fractures on radiographs taken for clinical purposes, rather than to screen for the presence of MBDP. Fractures were noted at mean postnatal ages of 100.0 ± 61 days after birth and the most common sites were ribs (74%), followed by the humerus (19%) and femur (7%). A number of studies have examined the incidence of rib fractures in preterm infants, from the review of anteroposterior chest radiographs, performed for monitoring of lung disease in VLBW and ELBW infants. The reported incidence of radiologically apparent rib fractures in this group varied from 2% to 7% [5, 6].

In this review, we describe the comprehensive and multidisciplinary Neonatal Bone Health Programme (NBHP) that was implemented in 2015 at the neonatal intensive care unit at King Abdullah Specialized Children's Hospital, Riyadh, KSA (Fig. 1). This led to the virtual elimination of fragility fractures in VLBW and ELBW sick infants, over an 18 months period. Before discussing the NBHP, we briefly reviewed factors that result in impaired bone strength in VLBW and ELBW sick, preterm infants.

2. THE PATHOPHYSIOLOGY OF METABOLIC BONE DISEASE OF PREMATURITY (MBDP)

Two-thirds of total calcium and inorganic phosphorus is accrued by the fetus during the third trimester [7]. Thus, infants who are born preterm are deprived of these bone-forming minerals. Following birth, it is difficult to maintain a comparable intake of minerals, either by enteral feed or total parenteral nutrition, especially in VLBW and ELBW sick infants. Many of these infants take a protracted time to establish enteral feeds, which may be interrupted due to intolerance and bowel disorder, such as necrotizing enterocolitis. Such infants may require total parenteral nutrition (TPN), often for prolonged periods. It is difficult to provide

adequate quantities of minerals by this route because the solubility of calcium and phosphorus limits their concentrations in the TPN solution [8]. Medications, such as glucocorticoids, diuretics, and methylxanthines lead to bone resorption thus increasing the risk of fragility fractures [9]. Proton pump inhibitors used to treat gastroesophageal reflux disease may also increase the risk of fractures [10].

Postnatal immobilisation and loss of placental oestrogen also contribute to the development of MBDP. The impact of postnatal immobilisation needs to be considered in the context of Frost's mechanostat model as applied to intrauterine skeletal development [11, 12]. Briefly, Frost stated that bones adapt their strength to the mechanical forces that they are subjected to, which primarily arise from muscles. Such forces result in changes in the dimensions of the bone or 'strains', which are sensed by a regulatory feedback system in the bone called the "mechanostat". Thus, bones respond to increased loading by adding net bone at sites that are mechanically challenged, thereby keeping bone strains within the physiological limits. In the intrauterine environment, the loading of the fetal skeleton arises from the movement against the resistance of the uterine muscle [12]. The fetus is exposed to high placental oestrogen during intrauterine life, which lowers the mechanostat set point on endosteal bone surfaces and this causes cortical thickening through increased endocortical bone accrual [7, 13]. Following birth, unloading of the skeleton resulting from the cessation of resistance movements, together with loss of the placental oestrogen, leads to endocortical bone resorption and hence thinning of the cortex [13]. Mercy and colleagues longitudinally evaluate postnatal changes in the tibial speed of sound (which reflects cortical thickness and bone mineral density) and lower limb length (a measure of tibial growth) in 84 preterm infants (median gestation 26.8 weeks (range 23-35.2 weeks) and median birth weight 869.5 g (range 418-1481 g)) [7]. Over a median postnatal follow-up period of four weeks (3-16 weeks), lower limb length increased with postnatal age, indicating a continuing increase in tibial length after birth. In contrast, there was an overall decline in the tibial speed of sound with postnatal age. These observations are in keeping with observations made by Beyers *et al*, who using humeral radiogrammetry, observed progressive cortical thinning due to endocortical bone resorption [14, 15].

The importance of the role of physical activity in influencing bone mineral density in very low birth weight infants comes from trials of postnatal physical activity interventions. Moyer-Mileur and colleagues showed that a daily 5-to-10-minute programme of passive physical activity of the upper and lower extremities resulted in increased areal BMD, measured by DXA, in very low birth weight infants compared with a non-exercising control group [16]. These findings are supported by the systematic review of physical therapy to prevent MBDP in Preterm Infants by Toro-Ferrero *et al* [17].

Thus, MBDP is a multifactorial disorder arising from the disruption of bone mass accrual due to premature birth, postnatal immobilisation, and loss of placental oestrogen resulting in bone loss, inadequate provision of bone minerals from

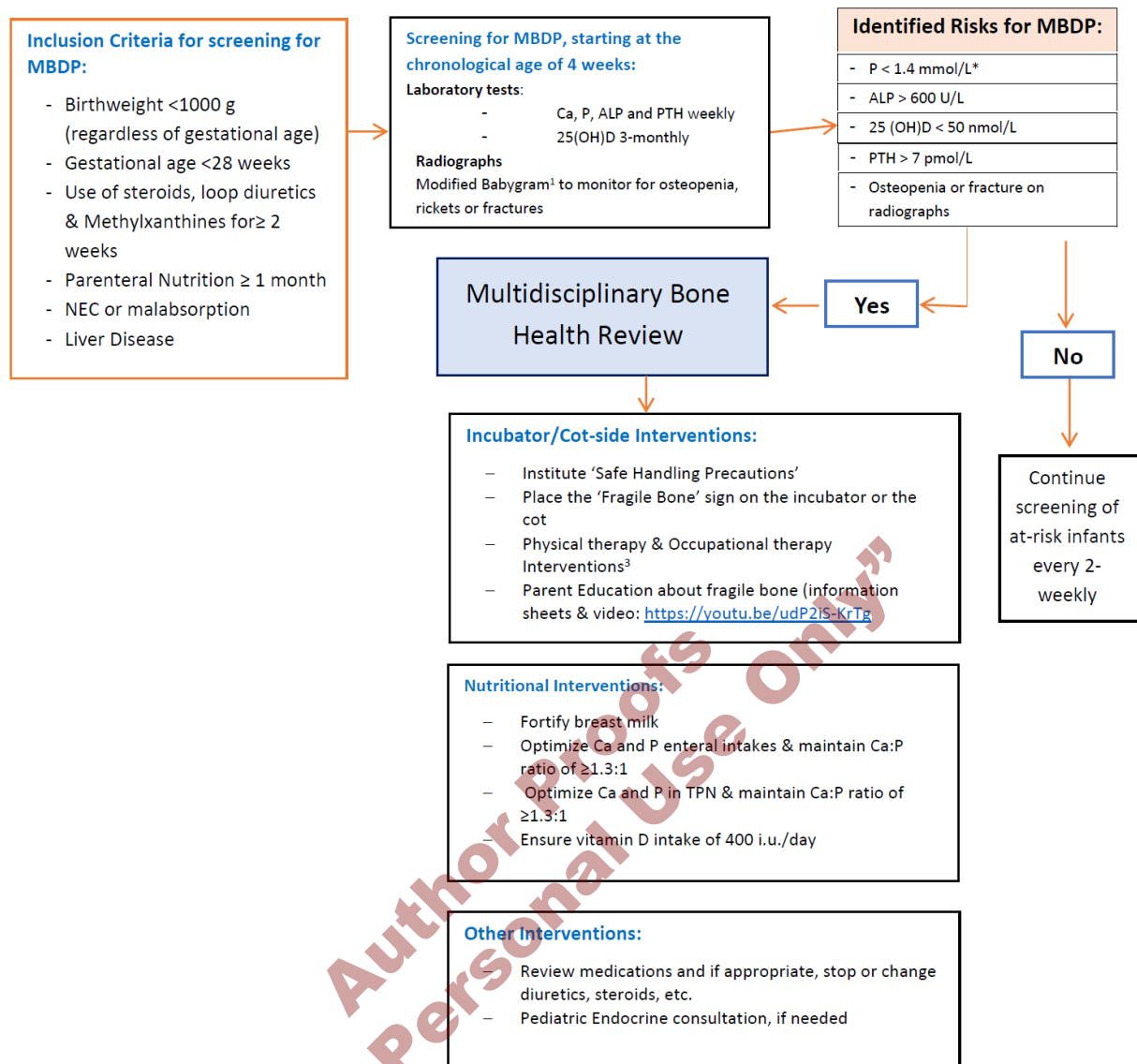


Fig. (1). The algorithm for screening & management of metabolic bone disease of prematurity at the Neonatal Intensive Care Unit, King Abdullah Specialized Children's Hospital. *Serum phosphate level used as a cut point for identifying a risk of MPDB may vary in different NICUs. **Abbreviations:** MBDP, Metabolic Bone Disease of Prematurity; NEC, necrotizing enterocolitis; TPN, Total Parenteral Nutrition. Ca, calcium; P, phosphorus; ALP, alkaline phosphatase; PTH, parathyroid hormone; 25(OH)D, 25 hydroxyvitamin D. (A higher resolution / colour version of this figure is available in the electronic copy of the article).

enteral and parenteral nutrition, and medications that leach out bone minerals from the skeleton. All these factors lead to skeletal demineralisation and a decrease in bone strength with the attendant risk of fragility fractures.

3. THE ROLE OF CALCIUM TO PHOSPHATE RATIO IN ENTERAL & PARENTERAL NUTRITION IN EXACERBATING MBDP

In addition to providing quantities of calcium and phosphate that are close to intrauterine accretion rates for these minerals, it is equally important to maintain the optimum calcium-to-phosphate ratio, in milligram to milligram, in enteral feeds and parenteral nutrition. Ideally, the calcium-to-phosphate ratio of enteral and parenteral feeds should be maintained around 1.5:1 to 1.7:1. Early publications on the

pathogenesis of MBDP highlighted the role of phosphate deficiency in the pathogenesis of MBDP, particularly in those infants fed on human breast milk [18, 19]. Thus, the provision of phosphate supplements to preterm infants is not an uncommon practice that is used to prevent or treat MBDP [20]. This results in a lower calcium-to-phosphate ratio, which leads to mild and transient hypocalcaemia (low ionised calcium concentration) and elevated serum parathyroid hormone levels. The resulting secondary hyperparathyroidism leads to subperiosteal bone resorption, reduced cortical thickness, increased cortical porosity, and a further reduction in bone strength caused by endocortical bone resorption [7]. It also results in increased renal tubular loss of phosphate and hypophosphatemia. Chronic hypophosphatemia leads to impaired mineralisation of the growth plate and osteoid, thus

resulting in **rickets-like** changes on radiographs of infants with MBDP, who are treated with phosphate supplements with the provision of calcium supplements to maintain the optimal calcium-to-phosphate ratio in enteral/parenteral feeds [21].

4. THE DIAGNOSIS OF MBDP

MBDP is rarely associated with clinical features, except when there is a limb deformity or visible/palpable callus due to bone fracture(s). Overt manifestations of rickets (frontal bossing, craniotables, swelling of wrists, ankles & costochondral junctions) are rare. In the clinical setting, the diagnosis is usually based on **the** radiological and biochemical features of MBDP.

Plain radiographs are insensitive **to** detecting osteopenia due to mineral deficiency. An old study in adults showed that 20-40% of bone mineral content has to be lost before osteopenia becomes apparent on radiographs [22]. However, a recent systematic review of the literature did not support this assumption in relation to radiographs of 0 to 2-year-old children [23]. Radiological signs of secondary hyperparathyroidism, when present include subperiosteal bone resorption and occasionally cystic bone lesions due to "brown tumours". If a fracture is detected, then a limited skeletal survey may be necessary to identify other occult fractures. Koo and colleagues have graded MBDP based on **single-view** radiographs of wrists and ankles: stages:

Grade 1 - Loss of the density of the white line in the metaphyses, increased submetaphyseal lucency, and thinning of the cortex.

Grade 2 - Changes grade 1 and fraying of metaphyses, with splaying and cupping (radiological changes of rickets).

Grade 3 - Grade 2 changes plus fractures [24].

Unfortunately, measurement of bone mineral density by dual-energy X-ray absorptiometry, at the point of care in VLBW and ELBW is challenging due to the lack of scanners in neonatal units, difficulty scanning sick infants, and a lack of normative data. In research studies, radiogrammetry and quantitative ultrasound have been used for assessing bone health in preterm infants in research studies [7, 25].

Serum levels of phosphate, alkaline phosphate (ALP), and parathyroid hormone (PTH) are the most commonly used markers both for screening and diagnosis of MBDP [20, 21, 26]. Periodic measurement of serum 25-hydroxyvitamin D (25OHD), a reliable marker of an individual's vitamin D status, is also important to ensure that the preterm infant does not become vitamin D deficient. Serum ALP, which is a biochemical marker of bone turnover, is often raised in preterm infants with MBDP. The American Academy of Pediatrics Committee on Nutrition recommends screening all VLBW infants for MBDP with serum phosphate and ALP measurements, starting at the age of 4 to 5 weeks after birth [26]. Rayannavar & Calabria reported that serum ALP levels ≥ 900 IU/l had 100% sensitivity and 70% specificity for MBDP [27]. However, serum ALP levels are affected by the assay used to measure it and its level may be raised in infants with liver disease. Recently, Moreira *et al* and Chinoy *et al*

have emphasised the importance of measuring serum PTH levels, as it reflects dietary calcium deficiency or suboptimal **calcium-to-phosphate** ratio in enteral or parenteral feeds [21, 28].

5. THE PREVENTION OF MBDP & THE NEONATAL BONE HEALTH PROGRAM

Prevention of MBDP involves the provision of enteral nutrition and parenteral nutrition that meet intrauterine bone mineral accrual rate, where possible limiting the use of medications that leach **minerals** from the skeleton, and **implementing** of a safe physical therapy program to minimise bone loss following the abrupt reduction in mechanical stimulation after birth.

King Abdulaziz Medical City (KAMC), National Guard Health Affairs, Riyadh is a large tertiary centre in Riyadh, Saudi Arabia, that serves East Riyadh a catchment area with a target population of 1.5 million; mainly represented by the employees of the National Guard. The annual number of deliveries in KAMC is approximately 7000. In 2015, we instituted a comprehensive Neonatal Bone Health Program (NBHP) in KAMC, the purpose of which was to reduce fragility fractures in high-risk neonates. This program is implemented by a multidisciplinary team consisting of Neonatologists, Pharmacists, Radiologists, Neonatal Nurses, Dietitians, Physiotherapists, Occupational therapists, and Paediatric Endocrinologists. The role of this team is to identify the at-risk preterm infants, screen for MBDP, and institute measures to support the mineralisation of the skeleton and ultimately reduce the risk of fragility fractures.

The prevention of MBDP by providing optimum enteral nutrition involves fortifying breast milk and the use of specific preterm formulae providing optimum levels of calcium and phosphate to support skeletal mineralisation [29]. As unfortified human milk does not contain enough minerals to meet the needs for bone mineralisation in preterm infants, it is important to fortify breast milk with commercially available multi-nutrient human milk fortifiers [30]. Occasionally, individualised mineral fortification may also be necessary to augment human breast milk's calcium and phosphate content. From nutritional consensus guidelines, current mineral recommendations for preterm infants are to provide 120 to 200mg/kg/day of calcium and 65 to 140mg/kg/day of phosphorous through enteral feeds [26, 29]. It is important to maintain the enteral calcium-to-phosphate ratio $\geq 1.3:1$, on a milligram-to-milligram basis, for optimal mineral absorption and retention.

The solubility of calcium and phosphate in total parenteral nutrition (TPN) may limit the provision of sufficient quantities of these minerals to support skeletal mineralisation in preterm infants [8]. The American Academy of Pediatrics 2014 recommends 60 to 80 mg/kg/day of Calcium and 46.5 to 60 mg/kg/day of phosphate *via* TPN [31]. In contrast, the European Society of Paediatric Gastroenterology, Hepatology and Nutrition Committee on Nutrition recommends 52 to 120 mg/kg/day of Calcium and 31 to 71.3 mg/kg/day of Phosphate, with an optimal Ca:P ratio between 1.3-1.7, milligram to milligram [32].

As vitamin D is important for the absorption of calcium and phosphate it is important to maintain serum 25-hydroxy-vitamin D concentration above 50 nmol/l. We recommend that all preterm infants should receive 400 international units (10 micrograms) of Cholecalciferol (vitamin D3) daily.

All infants enrolled in the NBHP are referred to neonatal physiotherapists and occupational therapists, who implement a safe physical therapy program to minimise bone loss following the loss of mechanical stimulation after birth. This involves undertaking a passive range of limb motion and gentle joint compression, for 5 to 15 minutes daily. Such a programme had been shown to improve bone mineralization in preterm infants [16, 17]. At the same time, the Neonatal therapy and nursing staff also implement a programme of safe handling of at-risk neonates, without compromising the skin-to-skin contact with parents (see Appendix 1). The parents are provided face-to-face training on safe handling, supplemented with printed educational materials and access to a video (<https://youtu.be/udP2iS-KrTg>).

The at-risk infants in the programme had single-view anteroposterior radiographs of the torso and limbs at 4 weeks and after 8 weeks from enrolment into the program or before discharge. Since its implementation in 2015, 442 at-risk preterm infants have benefited from the NBHP. Sites of bone fracture identified and associated neonatal risk factors will be presented in a separate manuscript, which is under preparation. Following the implementation of the NBHP in 2015, the fracture incidence reduced from 14 cases per year to 3 cases per year (78% drop) over 2 years. Since 2017, no fractures have been identified on prospective radiographic surveillance.

CONCLUSION

Very low birth weight and extremely low birth weight infants who go on to develop metabolic bone disease of prematurity (MBDP), especially with secondary hyperparathyroidism, are at risk of suffering fragility fractures. MBDP is a multifactorial disorder arising from the disruption of bone mass accrual due to premature birth, postnatal immobilisation, and loss of placental oestrogen resulting in bone loss, inadequate provision of bone minerals from enteral and parenteral nutrition, and medications that leach out bone minerals from the skeleton. Such fractures may occur from routine handling and procedures such as cannulation. Most fractures are asymptomatic and often come to light incidentally on radiographs performed for other indications. We have shown that the Neonatal Bone Health Program (NBHP), reduced fragility fractures in high-risk neonates, through optimising enteral and parenteral nutrition, including maintaining calcium-to-phosphate ratio $\geq 1.3:1$, in milligram to milligram, biochemical monitoring of MBDP, safe-handling of at-risk neonates, without compromising passive physiotherapy and skin-to-skin contact with parents.

CONSENT FOR PUBLICATION

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CONFLICT OF INTEREST

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APPENDIX 1

Safe Handling Precautions for Infants with Fragile Bones

A. Key points

- Individualized caregiving should be performed with 2 caregivers.
- Care should be provided according to the infant's condition and needs.
- All infants should be kept as calm as possible during handling. Use relaxed hands and do not use force against the infant's movements during procedures.
- Slow, gentle handling is essential to reduce the risk of fractures. Avoid pushing, pulling, twisting, bending, and compressing limbs. Do not apply excessive pressure across the limbs or on the joints.

B. Vital signs + growth measurements

Blood Pressure

1. Ensure 2 caregivers are available for blood pressure measurement.
2. Handle the infant with slow gentle movements, apply the cuff without twisting, pulling and bending the limbs.
3. After checking the blood pressure, remove the cuff in the same way.



Length Measurement

1. When measuring the length slide the tape measure along the baby from head to toe.
2. Do not stretch the legs straight to obtain the length.



Weighing

1. Swaddled weighing helps the infant to remain calm and conserve energy.
2. Weigh the blanket first - take note of the weight.
3. Swaddle the infant in the previously weighed blanket.
4. Gently move the infant to the scales so the infant and the blanket are weighed together.
5. Subtract the weight of the blanket from number shown - this gives you the true weight of the baby.
6. Gently move the infant back into their cot/incubator.



C. Diaper Change, Dressing, Bathing, Feeding and Positioning

Diaper Change

1. Ensure 2 caregivers are available for diaper changes.
2. Caregiver A will provide support to the infant in the form of containment and non-nutritive sucking, and will ensure that the infant's arms and hands are gently flexed towards the midline.
3. Caregiver B will slide hands underneath the buttocks. Do not lift the legs by the ankles. Avoid pulling (widely abducting) thighs to protect joints and femur. Place the clean diaper underneath the soiled diaper, clean the front area, then roll the baby into a side lying position to clean the buttocks and back.



Dressing and Swaddling

1. Infants with fragile bones should always be dressed in loose clothing. Avoid tight overall clothing.
2. Pull the material over the limb. Do not pull the limb through the clothing.
3. Be sure that all digits are through the opening before you begin pulling. Avoid getting a hand or foot caught in clothing.
4. When undressing, slowly ease the clothing over the extremity rather than pulling the extremity through.
5. Preferred clothing is overalls with exposed feet
6. Swaddle the baby gently with hands near face and mouth for self-regulation





Bathing

1. Ensure 2 caregivers are available for bathing. Bathing should be done with parents as much as possible.
2. Bathing can be a tiring activity. The baby may feel more relaxed during their bath if wrapped in a light sheet. This prevents the baby from sliding while wet and also helps to keep their arms and legs tucked in close to their body.
3. Swaddled bathing helps babies to conserve energy for feeding, interaction with caregivers and weight gain.

4. Prepare the basin with warm water, and make sure the clothes and diaper are ready.
5. Wash baby's head first and dry it with a towel, then gradually slide the baby in the water.
6. Do not use pressure while washing.



Feeding

1. Gently swaddle the infant in flexion.
2. Ensure the baby is cradled closely to the caregivers body or use the side-lying method with a pillow.
3. When using the 'side-lying' position have a pillow on your lap. Ensure that you can see the infant's face during feeding, and support the infant's back with your hand. A foot stool should be used to ensure a slightly upright position.
4. Do not hold the baby's neck and balance them on your knee.





Positioning

1. When lifting an infant with fragile bones, use open hands with wide spread fingers supporting back of the head and buttocks.
2. When lifting the baby from their bed to their parents, consider swaddling the baby so that limbs are contained during movement.
3. Maintain head in alignment with the body and do not allow the limbs to dangle.
4. When handling or positioning an infant with fragile bones, do so with slow, gentle movements.
5. Maintain a neutral alignment of the body and extremities.
6. Use your open hands and forearms to provide full support when moving or repositioning the baby.
7. Infants should not be picked up under the axilla or around the rib cage.
8. Do not swaddle the baby tightly. Allow for freedom of movement to promote strong bones. Arms should be flexed towards the midline and/or near the face to promote self-regulation abilities.
9. Nesting can help to support the infant's body and limbs if fitted properly with less pressure. Use positioning aids to support the patient's position.



Timing of Care Giving

1. Parental participation is an essential part of nursing care and caregiving should be planned with parents.
2. Cares should be individualized according to the infant's sleep state and medical needs.
3. Cares can be carried out every 6 hours.
4. Clinical judgment is recognized as an integral part of providing patient care (e.g. if the abdominal girth increases at 0900 hrs, it is important to recheck it before the next feed.)

D. Invasive procedures

Adequate pain management is essential before and during such procedures to keep the baby calm.

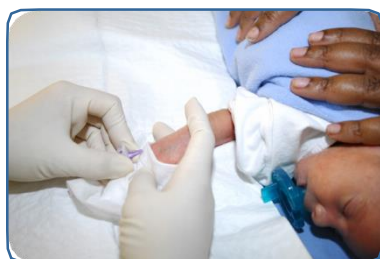
Intramuscular Injection

1. Take care to support the limb in a neutral position. Side lying position is preferable to supine.
2. Place a small blanket roll underneath the limb. Shape your hand to grasp the entire limb, putting your thumbs and fingers as shown below.
3. Make sure your fingers are close to the joint that you are moving.
4. Avoid pushing, pulling, twisting and bending limbs.
5. Do not apply excessive pressure across the limbs or on the joints.



Intravenous Cannula Insertion/Blood Sampling

1. Position the baby to maintain neutral alignment.
2. Moving the infant closer to you will help you to avoid the tendency to pull the limb.
3. In order to avoid twisting the limbs, reposition the baby to side lying or prone while searching for access.
4. Never push, pull, twist, or bend an extremity.



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